—Regular Article—

Dose Conversion in Opioid Rotation from Continuous Intravenous Infusion of Morphine Hydrochloride Injection to Fentanyl Patch in the Management of Cancer Pain

Chihiro KAWANO,*[,a,b] Takeshi HIRAYAMA,[a,b] and Masakazu KUROYAMA[a,b]

[a]*Pharmacy Practice and Science II (Kitasato University East Hospital), School of Pharmacy, Kitasato University, 5–9–1 Shirokane, Minato-ku, Tokyo 108–8641, Japan and* [b]*Department of Pharmacy, Kitasato University East Hospital, 2–1–1 Asamizodai, Minami-ku, Sagamihara, Kanagawa 252–0380, Japan*

(Received July 27, 2010; Accepted November 26, 2010; Published online December 7, 2010)

Opioid rotation has been proposed for management of cancer pain. No studies directly investigating dose equivalence between morphine injection (continuous IV administration) and the transdermal fentanyl patch have been reported. Therefore, we examined dose conversion ratios in patients undergoing opioid rotation from morphine injection to fentanyl patches. The subjects consisted of 45 patients admitted to Kitasato University East Hospital. Medical records were consulted to determine the ''basic dose of morphine injection immediately prior to rotation'' and the ''basic dose of fentanyl patch after rotation''. Equivalent doses and conversion ratios obtained with the expression of (daily dose of morphine injection (mg)/daily delivered dose of fentanyl patch (mg)) were determined from the relationship between the data by regression analysis. The regression equation obtained was $Y=50.882X-13.96$, $r^2=0.8922$, where X and Y are daily doses of morphine injection and fentanyl patch, respectively. Equivalent doses and conversion ratios for daily dose of morphine injection (mg): daily delivered dose of fentanyl patch (mg) (patch dose mg/3 days) were 16.6 mg: 0.6 mg (2.5 mg) = 28 : 1, 47.1 mg: 1.2 mg (5 mg) = 39 : 1 and 169.2 mg : 3.6 mg (15 mg) = 47 : 1. In other reports, the ratio of morphine *vs*. fentanyl at 50 : 1 had no relation to the dose. While the present study suggested that in opioid rotation from low dose, 50 : 1 is not enough for the fentanyl patch. The dose conversion ratio of morphine injection to fentanyl patch was different at the low doses and high doses of morphine.

Key words——dose conversion; opioid rotation; morphine hydrochloride; fentanyl patch; cancer pain

INTRODUCTION

The concept of ''opioid rotation'', is defined as ''When pain is relieved inadequately by opioid analgesics given in a dose that causes intolerable side effects despite routine measures to control them, treatment with the same opioid by an alternative route or with an alternative opioid administered by the same route should be considered''.[1,2] Whereas cancer pain has long been treated with multiple opioids outside of Japan, morphine has been the only strong opioid available for use for cancer pain in Japan until recently. However, the options for strong opioids in Japan were increased with the marketing of the fentanyl patch in 2002 and the controlled-release oxycodone hydrochloride tablet in 2003, the expansion of the indications for fentanyl citrate injection in 2004, and the marketing of oxycodone hydrochloride powder in 2006. This increase in the opioids available to treat cancer pain in Japan has also been accompanied by an increase in opioid rotation.[2,3]

In opioid rotation, the use of alternative opioids, dosage forms, and routes require that dose be adjusted for equianalgesic effect between opioid preparations. Dose conversion between opioid preparations is therefore essential, and a number of studies on dose conversion ratios between preparations have been published.[4–12] No studies directly investigating dose equivalency in opioid rotation with morphine hydrochloride injection given through continuous intravenous administration (hereafter, morphine injection (continuous IV administration)), which is commonly overused in clinical practice, and the transdermal fentanyl patch (hereafter, fentanyl patch) have, however, been published. We therefore investigated the dose conversion ratio in patients undergoing opioid rotation from morphine injection (continuous IV administration) to fentanyl patch and found a difference in the dose conversion ratio at low and high doses.

*e-mail: c-kawano@kitasato-u.ac.jp

METHODS

Eligible Patients Eligible patients included those with digestive system cancer undergoing opioid rotation from morphine injection (continuous IV administration) to fentanyl patch in the Gastrointestinal Unit of Kitasato University East Hospital from October 2003 to October 2008 who were on a stable dose of fentanyl patch within 10 days of rotation and experienced a difference of one or less in number of rescue doses required for pre- and post-rotation for three consecutive days. Patients requiring four or more rescue doses per day were excluded, and patients with biochemical test values corresponding to grade 3 or higher in ''Common Terminology Criteria for Adverse Events (CTCAE)'' were excluded to minimize the impact of pharmacokinetic variability on dose conversion ratios. This study was approved by Kitasato University Medical Ethics Committee.

Parameters Studied Basic patient information (age, sex, weight, and diagnosis), values of biochemical parameters indicative of hepatic and renal function measured immediately prior to opioid rotation (total protein, serum albumin, total bilirubin, direct bilirubin, AST, ALT, BUN, serum creatinine) and purpose of opioid rotation were obtained from the patient medical records.

Parameters related to opioid usage consisted of the daily dose of morphine injection (continuous IV administration) from immediately prior to rotation to 10 days after rotation (base prescribed dose), 3-day fentanyl patch dose (base patch dose), and the number of rescue doses per day. The daily delivered dose (base delivered dose) was then calculated from the base fentanyl patch dose based on the guideline in the package insert ''fentanyl patch dose of 2.5 mg/3 days = fentanyl patch delivered dose of 0.6 mg/day''.[13]

Method of Determining Dose Conversion Ratios Equivalent doses and conversion ratios were calculated for eligible patients by regression line analysis from the relationship between the ''base prescribed dose of morphine injection (continuous IV administration) immediately prior to opioid rotation'' and the ''base fentanyl patch delivered dose after opioid rotation''. The statistical analysis software SPSS® 12.0 J for Windows® was used for statistical computation.

RESULTS

A total of 51 subjects underwent opioid rotation from morphine injection (continuous IV administration) to fentanyl patch during the term of the investigation. Of these, six were excluded for grade 3 or higher values in biochemical parameters indicative of hepatic or renal function, leaving 45 eligible subjects.

The underlying diseases of the eligible subjects were: gastric cancer in 16 subjects, colorectal cancer in 10 subjects, pancreatic cancer in 8 subjects, anal canal cancer in 2 subjects, esophageal cancer in 3 subjects, bile duct cancer in 5 subjects, and hepatocellular carcinoma in 1 subject. The subjects included 28 males and 17 females with an age of 65.0±12.4 years, 35 to 87 years (mean±S.D., min to max) and weight of 47.1±8.2 kg, 32.9 to 73.7 kg. The purpose of opioid rotation was ''discharge'' in 37 subjects, ''avoidance of adverse effect'' in 6 subjects, ''reduction of fluid volume'' in 1 subject, and ''removal of peripheral line'' in 1 subject, and all of the subjects achieved good pain control. The dose of morphine injection (continuous IV administration) prior to rotation was 60.7±55.4 mg, 10 to 200 mg, and the fentanyl patch dose and fentanyl patch delivered dose after rotation were 6.1±4.3 mg 2.5 to 17.5 mg and 1.5 ±1.0 mg, 0.6 to 4.2 mg respectively.

The relationship between the base prescribed dose of morphine injection (continuous IV administration) prior to rotation and the fentanyl patch delivered dose after rotation is shown in Fig. 1. Analysis yielded a regression equation of $Y=50.882X-13.96$, $r^2=0.8922$, where X and Y are daily doses of morphine injection and fentanyl patch, respectively, indicating a very strong correlation. The equivalent doses and conversion ratios calculated from the regression equation are shown in Table 1.

The equivalent doses and conversion ratios in opioid rotation from morphine injection (continuous IV administration) to fentanyl patch in terms of base morphine injection (continuous IV administration) prescribed dose/base fentanyl patch delivered dose (base patch dose) were 16.6 mg : 0.6 mg (2.5 mg) = 28 : 1, 47.1 mg : 1.2 mg (5 mg) = 39 : 1, 77.6 mg : 1.8 mg (7.5 mg) = 43 : 1, and 169.2 mg : 3.6 mg (15 mg) = 47 : 1.

Non-opioid analgesics were concurrently administered in 27 subjects (63.0%) : NSAIDs in 23, carbamazepine in 1, chlorpromazine hydrochloride in

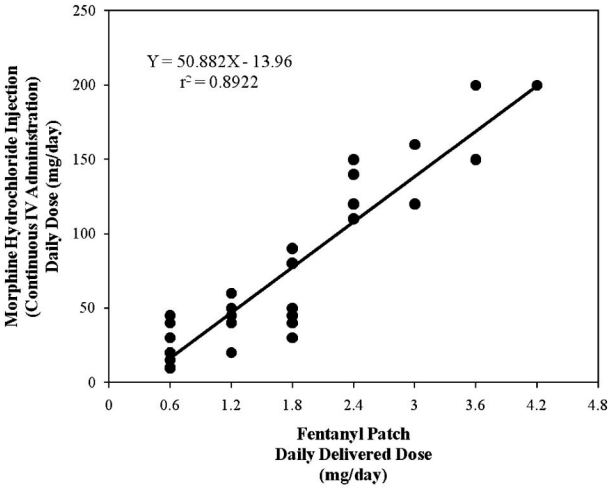

Fig. 1. Relationship between the Base Prescribed Dose of Morphine Injection (Continuous IV Administration) prior to Rotation and the Fentanyl Patch Delivered Dose after Rotation in 45 Subjects
$Y=50.882X-13.96$, $r^2=0.8922$.

Table 1. Equivalent Doses and Conversion Ratios between Continuous Intravenous Morphine and the Fentanyl Patch

Fentanyl patch[a]	Morphine injection dose (mg/day)	Conversion ratio of morphine : fentanyl[b]
0.6(2.5)	16.6	28 : 1(6.6 : 1)
1.2(5.0)	47.1	39 : 1(9.4 : 1)
1.8(7.5)	77.6	43 : 1(10.3 : 1)
2.4(10)	108.2	45 : 1(10.8 : 1)
3.0(12.5)	138.7	46 : 1(11.1 : 1)
3.6(15)	169.2	47 : 1(11.3 : 1)
4.2(17.5)	199.7	48 : 1(11.4 : 1)

[a] Shown as delivered dose (mg/day) and patch dose (mg/3 days) in parenthesis. [b] Shown as ratio to delivered dose (mg/day) and ratio to patch dose (mg/3 days) in parenthesis.

1, steroid in 5, neurotropin in 1 and bisphosphonate in 1.

DISCUSSION

Two studies on the dose conversion ratio between the fentanyl patch and morphine preparations have been published. Kato *et al.* calculated the conversion ratio from the regression equation obtained from the daily oral morphine dose prior to rotation and daily fentanyl patch delivered dose in subjects undergoing opioid rotation from oral morphine to fentanyl patch ($r^2=0.686$), reporting a daily oral morphine dose/daily fentanyl patch delivered dose ratio of 78 : 1.[4] Donner *et al.* similarly reported a daily oral morphine dose/daily fentanyl patch delivered dose ratio of 70 : 1 from the regression equation obtained from subjects undergoing opioid rotation from oral morphine to fentanyl patch ($r^2=0.827$), concluding that a 100 : 1 ratio was appropriate with allowance of a safety margin.[5] The U.S. package insert for the fentanyl patch gives a somewhat higher dose conversion ratio of 150 : 1 for oral morphine and the fentanyl patch,[11] but does not state how this ratio was derived. Whereas the publications discussed above have investigated dose conversion ratios in subjects undergoing opioid rotation from oral morphine to fentanyl patch, there are no published studies in subjects undergoing opioid rotation from morphine injection (continuous IV administration) to fentanyl patch.

Injectables are frequently overused in the management of cancer pain in in-patients, because they allow for easy dose adjustment and provide a rapid analgesic effect.

Given the lack of published studies, the method currently used for dose conversion between morphine injection (continuous IV administration) and the fentanyl patch consists of use of two conversion ratios between oral morphine and the fentanyl patch and between oral morphine and morphine injection (continuous IV administration). In short, the conversion ratio of 50 : 1 between morphine injection (continuous IV administration) and the fentanyl patch routinely used in clinical practice is calculated from the 150 : 1 conversion ratio between oral morphine and the fentanyl patch given in the fentanyl patch package insert and a 3 : 1 conversion ratio between oral morphine and morphine injection (continuous IV administration).

However, the absolute bioavailability of morphine (F) varies from approximately 20 to 40%.[10] This is because the hepatic extraction rate (Eh) of morphine is 1.3 based on the morphine pharmacokinetic parameters of unchanged drug urinary excretion rate (Ae) of 8%,[14] systemic clearance (CL) of 1050 ml/min,[14] and distribution volume (Vd) of 1.1 l/kg to 5.3 l/kg,[15,16] indicating a dependence on hepatic metabolism and blood flow. To estimate blood concentration variability, then, total blood concentration during oral administration is determined through $Cpss=(Fa\cdot D/\tau)/(fuB\cdot CLintH)$, with blood concentrations increasing with reduced hepatic clearance (CLintH) from degeneration of hepatic parenchymal cells (reduced liver function, including increased AST and ALT). Total blood concentration during con-

tinuous IV administration is determined through Cpss = Rinf/Qh, with hepatic blood flow, while CLintH is not the determining factor in blood concentration variability. In addition, during continuous IV administration, all of the administered drug passes into general circulation. Therefore, reduced CLintH greatly affects the amount of drug that passes into circulation, resulting in individual differences in bioavailability during oral administration, while reduced CLintH does not give rise to individual differences during continuous IV administration. This discussion precludes simple calculation of an exact dose conversion ratio between oral morphine and morphine injection (continuous IV administration) and accounts for the variability encountered in the literature, including the 1 : 2 to 1 : 3 oral dose/continuous IV dose ratio reported by Hanks *et al.*[10] and the 1 : 6 oral dose/continuous IV dose ratio reported by Foley.[17] It is, then, more appropriate to determine the dose conversion ratio between morphine injection (continuous IV administration) and the fentanyl patch directly through the dose of morphine injection (continuous IV administration) rather than through conversion from oral morphine dose to morphine injection (continuous IV administration) dose.

In the current study, the dose conversion ratio at which pain control was achieved after rotation was determined in subjects undergoing rotation from morphine injection (continuous IV administration) to fentanyl patch. Subjects with worsened renal or hepatic function were subsequently excluded from eligibility to minimize the impact of pharmacokinetic variability.

The results of the study showed morphine injection (continuous IV administration)/fentanyl patch dose conversion ratios of 28 : 1 for a 0.6 mg base fentanyl patch delivered dose (base patch dose of 2.5 mg), 43 : 1 for a 1.8 mg base fentanyl patch delivered dose (base patch dose of 7.5 mg), and 47 : 1 for a 3.6 mg base fentanyl patch delivered dose (base patch dose of 15 mg). The conversion ratio of morphine injection (continuous IV administration) to fentanyl patch thus increased with increasing dose. In contrast, the fentanyl patch (Durotep patch®) package insert recommends "conversion from an oral morphine dose of 90 mg/day (45 mg/day for suppository, 30 mg/day for injection) to a fentanyl patch dose of 2.5 mg/3 days (delivered dose of 0.6 mg/day)".[18] This examination yields a uniform dose-independent conversion ratio of morphine injection (continuous IV administration) dose 30 mg/day/fentanyl patch delivered dose 0.6 mg/day = 50 : 1.

The results of our study suggested that the fentanyl patch dose may be inadequate in opioid rotation from morphine injection (continuous IV administration) to fentanyl patch conducted according to the guideline in the fentanyl patch package insert in subjects achieving pain control at low doses. When the analgesic effects of co-administered drugs are contributory factors, the calculated conversion ratio is considered to be larger than the recommended conversion ratio. Therefore, there should be no impact of co-administered drugs.

This in turn suggests that a uniform conversion ratio calculated independently of dose, such as those in the studies on dose conversion ratios,[4,5] may not always be appropriate, while the equivalent dose may in fact be required to be modified in accord with dose. Issues with absorption of fentanyl patches, fentanyl and morphine pain thresholds, and development of tolerance to the analgesic effect of morphine may be contributory factors in this finding, although further study into the underlying causes is required.

After rotation, none of the eligible subjects of the study required dose reduction or discontinuation due to adverse reactions, and pain relief was promptly achieved within 3–10 days after rotation to fentanyl patches. Accordingly, the obtained conversion ratio herein was thought to be appropriate from the perspectives of efficacy and adverse reactions.

The results of our study suggested that the fentanyl patch dose may be inadequate in opioid rotation from morphine injection (continuous IV administration) to fentanyl patch conducted according to the guideline in the fentanyl patch package insert in subjects achieving pain control at low doses. We believe that the adoption of the obtained conversion ratio will result in immediate pain relief.

Even in high-dosage subjects, the obtained value was nearly equivalent to the recommended conversion ratio, and therefore, safe and prompt pain relief would be possible.

Our study shed light on dose equivalence and conversion ratios in rotation from morphine injection (continuous IV administration), which is commonly overused in clinical practice, to fentanyl patch. The results of our study may improve patient QOL (quality of life), because they allow for more rapid and ap-

propriate dose adjustment in opioid rotation from morphine injection (continuous IV administration) to fentanyl patch in patients with cancer pain.

REFERENCES

1) Mercadante S., *Cancer*, **86**, 1856–1866 (1999).
2) Maruyama K., Yokochi W., Utsunomiya H., *Pain Clinic*, **24**, 12571–265 (2003).
3) Doi T., Shima Y., *Terminal Care*, **13**, 5–10 (2003).
4) Kato K., Mizaki T., Yamazaki S., Nitta M., Hasegawa M., Kamiya Y., Hosoda R., *Yakugaku Zasshi*, **124**, 287–291 (2004).
5) Donner B., Zenz M., Tryba M., Strumpf M., *Pain*, **64**, 527–534 (1996).
6) Kalso E., Vainio A., *Clin. Pharmacol. Ther.*, **47**, 639–646 (1990).
7) Bruera E., Belzile M., Pituskin E., Fainsinger R., Darke A., Harsanyi Z., Babul N., Ford I., *J. Clin. Oncol.*, **16**, 3222–3229 (1998).
8) Mosser K. H., *Am. Fam. Physician*, **45**, 2289–2294 (1992).
9) Anderson R., Saiers J. H., Abram S., *J. Pain Symptom Manage.*, **21**, 397–406 (2001).
10) Hanks G. W., Conno F., Hanna M., Kalso E., McQuay H. J., Mercadante S., Meynadier J., Poulain P., Radbruch L., Casas J. R., Sawe J., Twycross R. G., Ventafridda V., *Br. J. Cancer.*, **84**, 587–593 (2001).
11) ''Physician's Desk Reference,'' 62nd ed., Thomson Healthcare Inc, Montvale, 2008, pp. 2352–2358.
12) Heiskanen T., Kalso E., *Pain*, **73**, 37–45 (1997).
13) Mizuguchi T., Yamamura H., Takeda F., Hiraga K., Ariyoshi Y., Tsunetou S., *Iyaku Journal*, **37**, 2389–2402 (2001).
14) Glare P. A., Walsh T. D., *Ther. Drug Monit.*, **13**, 1–23 (1991).
15) Moore A., Sear J., Baldwin D., Allen M., Hunniset A., Bullingham R., McQuay H., *Clin. Pharmacol. Ther.*, **35**, 641–645 (1984).
16) Hoskin P., Hanks G. W., Aherne G. W., Chapman D., Littleton P., Filshie J., *Br. J. Clin. Pharmacol.*, **27**, 499–505 (1989).
17) Foley K. M., *N. Engl. J. Med.*, **313**, 84–95 (1985).
18) Drugs in Japan Ethical Drugs 2008, supervised by Drugs in Japan Forum, Jiho Inc., Tokyo, 2008, pp. 1977–1979.